Pesticide Exposure and Self-Reported Gestational Diabetes Mellitus in the Agricultural Health Study

Tina M. Saldana, phd[1]
Olga Basso, phd[1]
Jane A. Hoppin, scd[1]
Donna D. Baird, phd[1]

Charles Knott, mpa[2]
Aaron Blair, phd[3]
Michael C.R. Alavanja, drph[3]
Dale P. Sandler, phd[1]

OBJECTIVE — To examine the association between pesticide use during pregnancy and gestational diabetes mellitus (GDM) among wives of licensed pesticide applicators.

RESEARCH DESIGN AND METHODS — Using data from the Agricultural Health Study (AHS), we estimated the association between self-reported pesticide-related activities during the first trimester of the most recent pregnancy and GDM among 11,273 women whose pregnancy occurred within 25 years of enrollment.

RESULTS — A total of 506 (4.5%) women reported having had GDM. Women who reported agricultural pesticide exposure (mixing or applying pesticides to crops or repairing pesticide application equipment) during pregnancy were more likely to report GDM (odds ratio [OR] 2.2 [95% CI 1.5–3.3]). We saw no association between residential pesticide exposure (applying pesticides in the home and garden during pregnancy) and GDM (1.0 [0.8–1.3]). Among women who reported agricultural exposure during pregnancy, risk of GDM was associated with ever-use of four herbicides (2,4,5-T; 2,4,5-TP; atrazine; or butylate) and three insecticides (diazinon, phorate, or carbofuran).

CONCLUSIONS — These findings suggest that activities involving exposure to agricultural pesticides during the first trimester of pregnancy may increase the risk of GDM.

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G estational diabetes mellitus (GDM) is a common complication of pregnancy, affecting ff4% of pregnancies in the U.S. (1). Occurrence in the U.S. and worldwide differs by ethnicity, ranging between 1 and 14%, reflecting population-specific patterns seen for type 2 diabetes (2). GDM is regarded as an early stage in the progression to type 2 diabetes and has similar risk factors (3). Known risk factors for GDM include obesity, older maternal age, higher parity, having had GDM or a macrosomic infant in a previous pregnancy, and family history of diabetes (4,5).

Exposure to pesticides may result in abnormal glucose metabolism, increasing the risk of diabetes. In a cohort study of Australian outdoor workers, mortality from diabetes was elevated among those with high pesticide exposures compared with the general population (6). Studies of dioxin exposure (a contaminant of pesticides) are also suggestive of increased

risk for type 2 diabetes, hyperglycemia, and hyperinsulinemia (7–9). In addition, there have been several case reports of glycosuria and transient hyperglycemia associated with herbicide or insecticide poisoning (10–12). Furthermore, glucose metabolism disturbances have been observed with exposure to both organochlorine and organophosphate insecticides in animal and in vitro studies (13–15). These disturbances include an increase in insulin and blood glucose concentrations, as well as changes in the activity of glucose metabolism enzymes (16–18).

While studies have examined the relationship between pesticides and diabetes (16–18), none have focused on GDM. In the diabetogenic state of pregnancy, women may be particularly susceptible to environmental triggers affecting glucose metabolism. In this article we investigated the risk of developing GDM in relation to pesticide exposures among wives of farmers enrolled in the Agricultural Health Study.

RESEARCH DESIGN AND METHODS — The Agricultural Health Study (AHS) is a large study of licensed pesticide applicators and their families in Iowa and North Carolina. Farmers and commercial applicators using restricted-use pesticides must be licensed every 3 years. Between 1993 and 1997, 52,395 of those applying for a Private Pesticide License in Iowa and North Carolina enrolled in the AHS by completing a brief questionnaire. Seventy-five percent (32,171) of spouses also enrolled in the study by completing a different questionnaire (89.5% responded by mail and 10.5% by telephone). Of these, 61% (19,587) returned a Female and Family Health (FFH) questionnaire, with 18,335 reporting at least one pregnancy. The study was approved by the institutional review boards of the National Institutes of Health, the University of Iowa, and the Battelle Centers for Public Health Research and Evaluation. Additional details of the study are provided elsewhere (19).

Data for this study were obtained at the time of enrollment from both the ap-

plicators' and spouses' questionnaires (available at http://www.agheath.org). The FFH questionnaire provided information on reproductive health, including pregnancies that occurred before enrollment in AHS. Detailed information on pregnancy complications and exposure history was collected on the most recent pregnancy. We excluded women whose pregnancy had occurred ffi25 years before enrollment in the study (*n* ffl 5,272), women whose age at the most recent pregnancy was missing (*n* ffl677), and women recorded as aged ⌐ 16 or ffi49 years (*n* ffl 17) at the time of the pregnancy. We also excluded women whose pregnancy ended in a miscarriage, induced abortion, molar, or ectopic pregnancy(*n* ffl 724)oriftheoutcomewasnot reportedandthepregnancydidnotreach 37 weeks of gestation (*n* ffl 104). Further exclusions included women reporting diabetes diagnosed before the age of 20 years (*n* ffl 46) and those with missing data on either GDM, pesticide-related activities during pregnancy, or other covariates of interest (*n* ffl 222). After these exclusions, 11,273 pregnancies remained for analysis.

Outcome definition

Information on pregnancy complications was only obtained for the most recent pregnancy. We categorized women as havinghadGDMiftheyanswered"yes"to the question, "Did you have gestational diabetes (diabetes just during pregnancy) during this pregnancy?"

Exposure classification

To examine pesticide use, we used self-reportedinformationfromtheFFHques-tionnaire about pesticide-related activities during the first trimester of the most recent (index) pregnancy. Expo-suresduringthesecondandthirdtrimes-ters were not ascertained. We defined four ordered pesticide exposure categories by combining activities with similar potential for pesticide exposure. The re-sultingcategories,fromlowesttohighest, were: *1*) no exposure, *2*) indirect exposure (planting, pruning, weeding, picking, or harvesting), *3*) residential exposure (applying pesticides to garden or inside house), and *4*) agricultural exposure (mixing, applying pesticides to crops, or repairing pesticide application equipment). Women who reported activ-itiespertainingtomorethanonecategory were classified according to the category reflecting the highest exposure potential.

Data on specific pesticide use during pregnancy were not collected. To explore thepossibleroleofspecificpesticides,we examined the association between GDM andthewomen'sself-reportedever-useof 50 individual pesticides. Our sample for these analyses was restricted to women whowereclassifiedintheagriculturalex-posure category during the index pregnancy. We report only those pesticides of a priori interest (2,4,5 T; 2,4,5 TP/silvex; and malathion), based on the existing studies (7–9) and those with at least five exposed cases.

Statistical analysis

Weusedunconditionallogisticregression models to estimate the odds ratios (ORs) of GDM as a function of pesticide exposure. We adjusted for BMI at enrollment (prepregnancy BMI was not available), mother's age at delivery, parity at the beginning of the pregnancy (previous live birthsandstillbirths),andrace.Theseco-variates were decided a priori based on their being known predictors of GDM. We also adjusted for study center (Iowa andNorthCarolina).Additionally,forthe models including women's ever-use of pesticides, where appropriate, we adjusted for the five most common pesticides reported by women in the AHS (glyphosate; carbaryl; malathion; 2,4-D; and diazinon) (20). For our analyses, we used the AHS Phase 1 Release P1REL0310.01 data. All statistical analy-seweredoneusingSASversion9.1(21).

RESULTS — A total of 506 of 11,273
women (4.5%) reported having GDM in theirmostrecentpregnancy.Ofthestudy participants, ffi97% were white and ffi50% had greater than high school education (Table 1). Women aged ffi30 years at the time of the index pregnancy were more likely to report GDM. Women with GDM were more likely to report a BMI ffi25.0 kg/m² at the time of enrollment (47%) compared with women without GDM(40%).Therewerenodifferencesin parity or smoking status between women with and without GDM. Over half the women reported that they had mixed or applied pesticides at some time in their life(57%),andtheproportionwassimilar for those with and without GDM. GDM was more common among women from North Carolina than among women from Iowa. The mean interval between enrollment and the most recent (index) pregnancy was 11.7 years.

Women whose activities during the

firsttrimesterofpregnancyinvolvedagri-cultural exposures (mixing or applying pesticides or repairing pesticide-related equipment) had a twofold increased risk of developing GDM (adjusted OR 2.2 [95% CI 1.5–3.3]) (*P* ⌐ 0.0001) (Fig. 1). We saw no increased risk of GDM among women with residential exposures (ap-plyingtohomeorgarden)(1.0[0.8–1.3]) or with indirect exposures (planting, pruning,weeding,picking,orharvesting) (0.9 [0.7–1.1]) during the first trimester of pregnancy (Fig. 1). Women who re-portedhavingmixedorappliedpesticides at any time before enrollment in the AHS were not at increased risk of GDM compared with those who did not (data not shown).

Toreducethepotentialforinaccurate recall,werestrictedtheanalysistowomen whose pregnancies occurred within 12 years of enrollment (*n* ffl 6,004). The adjusted OR for the association between agricultural exposure and GDM was 2.0 (95% CI 1.3–3.4). In addition, when we stratified the analysis by state, results were also unchanged (data not shown).

Pesticide-specific ORs for ever-use of 15 pesticides among women categorized with agricultural exposures during the first trimester of pregnancy (*n* ffl 337) are shown in Fig. 2. Risk of GDM was significantly associated with reporting of ever-use of the herbicides 2,4,5-T; 2,4,5-TP; atrazine;andbutylateandtheinsecticides diazinon, phorate, and carbofuran.

CONCLUSIONS — Womenenrolled intheAHSwhoreportedactivitiesinvolv-ing agricultural pesticide exposures during the first trimester of their most recent pregnancyhadatwofoldincreasedriskof developing GDM. GDM risk was not increased among women who reported using pesticides only in the home and garden or who reported working in the fields. Prior analysis has shown that women in the AHS are involved in many aspects of farm work (22). Only mixing and applying pesticides during the first trimester of pregnancy was associated with GDM. Thus, the association we observed is unlikely to be due to some uncontrolled correlate of participation in general farm activities. We had no information on specific pesticide use during pregnancy. For completeness, however, we examined the association between having ever mixed or applied individual pesticidesatsometimebeforeenrollment and GDM only among women who reported agricultural exposures during the

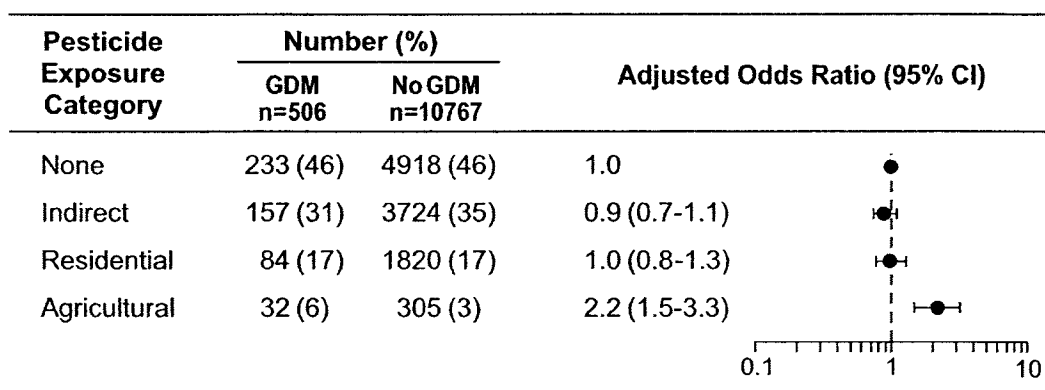**Table 1—*Characteristics of women with and without GDM in the AHS, 1993–1997***

Characteristics	GDM	No GDM	Crude OR (95% CI)
n	506	10,767	
Maternal age at pregnancy			
16–24	40 (8)	1,478 (14)	0.7 (0.5–0.9)
25–29	177 (35)	4,294 (40)	1.0
30–34	188 (37)	3,577 (33)	1.3 (1.0–1.6)
35–49	101 (20)	1,418 (13)	1.7 (1.3–2.2)
Race			
White	477 (94)	10,420 (97)	1.0
Other*	29 (6)	347 (3)	1.8 (1.2–2.7)
Education			
Less than high school	11 (2)	244 (2)	1.2 (0.6–2.3)
High school	149 (30)	3,589 (33)	1.0
More than high school	291 (57)	5,895 (55)	0.9 (0.5–1.7)
Missing	55 (11)	1,039 (10)	1.1 (0.6–2.0)
BMI at enrollment (kg/m²)			
< 18.5	8 (2)	193 (2)	1.2 (0.6–2.4)
18.5–24.9	164 (32)	4,620 (43)	1.0
25.0–29.9	142 (28)	2,698 (25)	1.5 (1.2–1.9)
ff30	97 (19)	1,607 (15)	1.7 (1.3–2.2)
Missing	95 (19)	1,649 (15)	1.6 (1.3–2.1)
Parity†			
0	71 (14)	1,243 (12)	1.0
1	182 (37)	4,187 (39)	0.8 (0.6–1.0)
2	158 (31)	3,232 (30)	0.9 (0.6–1.1)
3–	95 (19)	2,105 (19)	0.8 (0.6–1.1)
Smoking in pregnancy			
Did not smoke	449 (89)	9,643 (90)	1.0
Smoked	54 (11)	1,081 (10)	1.1 (0.8–1.4)
Missing	3 (< 1)	43 (< 1)	1.5 (0.5–4.9)
Ever mixed/applied pesticides‡			
No	209 (43)	4,462 (42)	1.0
Yes	282 (57)	6,163 (58)	1.0 (0.8–1.2)
State of residence			
Iowa	335 (66)	8,079 (75)	0.7 (0.5–0.8)
North Carolina	171 (34)	2,688 (25)	1.0

Data are *n* (%) unless otherwise indicated. *Other includes 167 individuals for missing race. †Parity includes live births and still births prior to the index pregnancy. ‡Total number varies due to 157 individuals missing.

index pregnancy. These analyses are, however, limited by the small sample sizes. An elevated risk of GDM was associated with ever-use of four herbicides, two organophosphate insecticides, and one carbamate insecticide. Since we do not have information on the timing of exposure relative to pregnancy, any resulting misclassification is likely to have biased these estimates toward null values.

Although our findings of an association between 2,4,5-T and 2,4,5-TP and GDM are based on small numbers, they are of particular interest given the potential for contamination with dioxin in these pesticides (23). Several biologic mechanisms have been proposed for the effects of dioxin-like compounds on glucose metabolism (24). In general, most effects are thought to be mediated through interactions between aryl hydrocarbon receptors and peroxisome proliferator-activated receptor-|–mediated signaling pathways (24), resulting in an increase in insulin resistance (14) and reduction in glucose transporter activity (15). Epidemiologic studies have also indicated an association between dioxin-like compounds and glucose metabolism (7–9,25). However, because these studies measured serum levels of TCDD (2,3,7,8 tetrachlorodibenzo-*p*-dioxin) after disease onset, it is possible that the disease process influenced TCDD metabolism. An advantage of questionnaire data in this instance is that our measure of pesticide exposure is unlikely to be influenced by disease processes.

Laboratory data have suggested a possible effect of malathion (an organophosphate) on glucose metabolism, including increases in insulin and blood glucose concentration and changes in key en-

Pesticide Exposure Category	Number (%)		Adjusted Odds Ratio (95% CI)
	GDM n=506	No GDM n=10767	
None	233 (46)	4918 (46)	1.0
Indirect	157 (31)	3724 (35)	0.9 (0.7-1.1)
Residential	84 (17)	1820 (17)	1.0 (0.8-1.3)
Agricultural	32 (6)	305 (3)	2.2 (1.5-3.3)

Figure 1—*Adjusted ORs for GDM and pesticide exposure category during pregnancy among wives of farmers in the AHS, 1993–1997. Models adjusted for BMI at enrollment, mother's age at pregnancy, parity, race, and state categorized as shown in Table 1. Indirect exposures include planting, pruning, weeding, picking, or harvesting. Residential exposures include applying pesticides to garden or inside house. Agricultural exposures include mixing or applying pesticides to crops or repairing pesticide application equipment.*
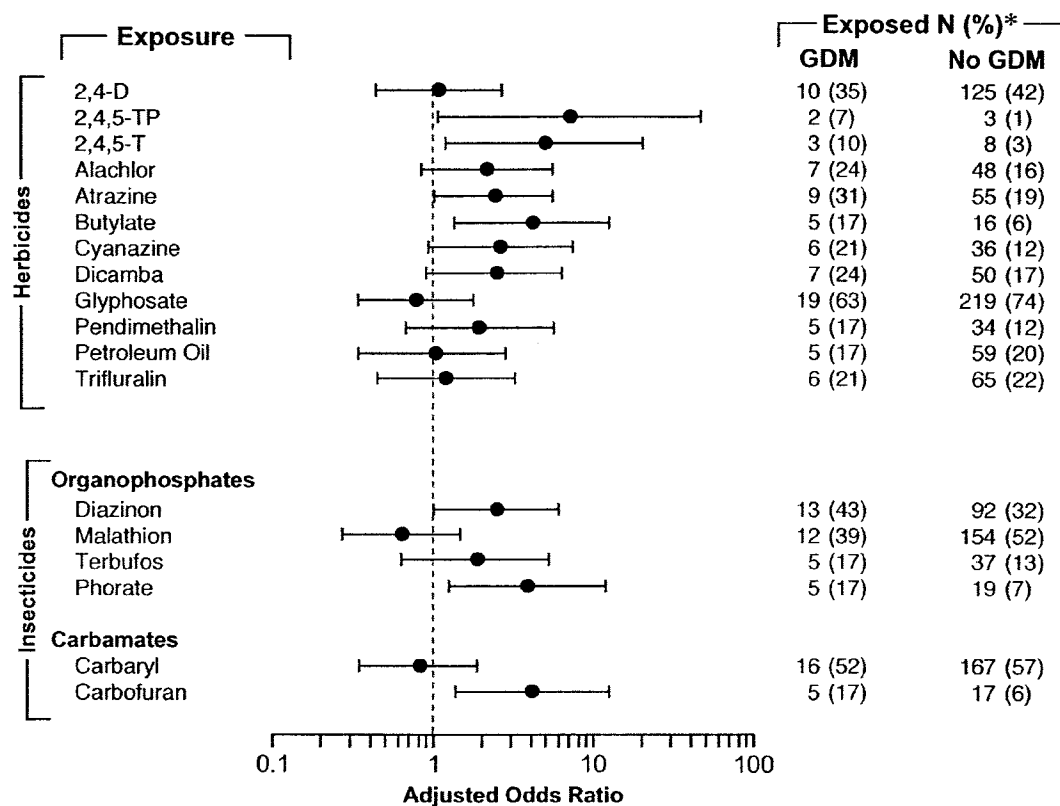
Figure 2—*Pesticide-specific ORs for GDM among wives of farmers in the AHS reporting agricultural exposure during pregnancy. Individual models adjusted for BMI at enrollment with categories of ⌐ 18.5 and 18.5–24.9 kg/m² combined, mother's age at pregnancy, parity, race, state, and commonly used pesticides by women. The numbers included in pesticide-specific analysis differ due to missing data. Among women who reported agricultural exposure during pregnancy, the number of women with GDM ranges from 29 to 32 and the number of women without GDM ranges from 281 to 297.*

zymes involved in gluconeogenesis, glycogenolysis, and glycolysis. Similar mechanisms may be involved for other organophosphates (16,17). In our study we did not find an increased risk of GDM among women who reported agricultural exposures during pregnancy and ever-use of malathion (Fig. 2). Malathion is widely used for home and garden as well as for crop applications, and its purchase does not require a pesticide license (20). It is possible that we missed an association with malathion by focusing solely on women who reported mixing or applying pesticides to crops during the first trimester of the pregnancy. However, when we examined women reporting home and garden use of pesticides during the first trimester we still failed to see an association.

We saw an increased risk of GDM associated with two other organophosphate insecticides (diazinon and phorate) and one carbamate insecticide (carbofuran). Interestingly, there have been several case reports of glycosuria with and without hyperglycemia following pesticide poisoning with organophosphate insecticides and carbamates (10–12).

This study provides data on a large number of women who reported performing specific tasks during the first trimester of their most recent pregnancy. Even though GDM in this study was self-reported, the reported frequency of 4.5% is in the expected range for the U.S. (3–5%) (4). Although our analysis excluded women with diabetes diagnosed aged ⌐ 20 years, we were unable to exclude preexisting type 2 diabetes for all women, since age at diagnosis of type 2 diabetes was asked in broad categories. Our GDM question asked specifically about "diabetes only during pregnancy" to facilitate more accurate reporting. Even so, bias from self-reported GDM may be a concern. Several studies in diverse populations have shown that maternal recall of rare obstetric complications (including GDM) is relatively accurate when compared with medical records (26–28). These studies report high sensitivity, which suggests that there are not likely to be unreported cases among the control subjects. While some women who report GDM may not have it, this would tend to bias our results toward the null.

The data on reported pesticide exposure during pregnancy span 25 years, which may affect accuracy of exposure reporting. However, we have previously found that farmers and their families tend to reliably report pesticide exposure history (29–31). Furthermore, our estimates were unchanged when we restricted the analysis to pregnancies that occurred within 12 years of enrollment. Unfortunately, the sample size was too small to focus on a shorter interval.

Our estimates may be affected by reporting bias if women who had GDM tended to over-report agricultural pesticide use during pregnancy or if women who had been exposed were more likely to report GDM. This is unlikely since GDM was not the primary focus of the questionnaire, and we characterized the exposure by aggregating responses to several individual questions. Furthermore, the increased risk observed in our estimates was associated only with activities with a greater potential for exposure to farm pesticides, while we saw no increase in risk with other activities.

Although adjusting for BMI had little

effect on risk estimates, our ability to control for it was limited by the fact that we relied on weight reported at enrollment rather than before the index pregnancy. Even though BMI tends to track over time, BMI at enrollment will be a better surrogate for recent pregnancies than for those more distant in time. It was, however, reassuring that restricting the analysis to more recent pregnancies did not change the results. Furthermore, although BMI was not a confounder in our analysis, it was significantly associated with GDM. Due to small sample size, we were unable to explore whether race modified the association between agricultural exposure and GDM.

Pregnancy is a known diabetogenic state resulting from decreased insulin sensitivity (32,33). The inability to compensate for the decreased insulin sensitivity results in hyperglycemia above the normal pregnancy ranges. Although much is known about common risk factors for GDM, our understanding of whether and how environmental exposures may affect risk is still limited. Research shows that 20–50% of women with GDM will develop type 2 diabetes within 5–10 years (34). Thus, understanding any potential effect of environmental exposures on glucose tolerance during pregnancy may have substantial public health importance beyond the direct effects on GDM.

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